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SCIENTIFIC SECTION

A comparison of skeletal maturation in patients with tooth agenesis and unaffected controls assessed by the cervical vertebral maturation (CVM) index

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Objective: The aims of this study were to (1) investigate if there is a difference in skeletal maturation between tooth agenesis and control patients and (2) whether skeletal maturation is affected by the severity of tooth agenesis. The cervical vertebral maturation (CVM) index can be used to assess skeletal maturation.

Design: A retrospective cross-sectional study.

Setting: Eastman Dental Hospital, London, UK.

Methods and materials: A total of 360 cephalograms of patients aged 9–17 years (164 males and 196 females) allocated to four subgroups (mild, moderate and severe tooth agenesis patients, and controls) were assessed retrospectively. There were 90 patients in each of the four subgroups. The skeletal maturation of each subject was assessed both quantitatively and qualitatively using the CVM index. All patients in the study were either currently receiving treatment or had been discharged from the hospital.

Results: There was no statistically significant relationship between skeletal maturation and the presence of tooth agenesis. Furthermore, there was no statistically significant relationship between the skeletal maturity of patients and different severities of tooth agenesis.

Conclusions: The data obtained from this group of patients and using this measurement tool alone does not supply sufficient reason to reject the null hypothesis. However, it suggests that it is possible that no difference exists between the groups.

Key words: Cervical maturation index, tooth agenesis

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Introduction

Tooth agenesis is a condition involving the developmental absence of teeth with a prevalence of between 4.6% (males) and 6.3% (females) in the European Caucasian population.[1] The male to female ratio for European populations is 1 : 1.4. The aetiology of tooth agenesis is best described in terms of a polygenic multifactorial model and can be divided broadly into genetic factors, environmental factors or systemic manifestations.[2,3] Msx genes have roles in craniofacial and tooth development in mice and humans.[4–7] Studies have shown that dental development is delayed in patients with tooth agenesis and the delay is affected by severity.[8] Since the Msx family of genes, among others are common to tooth and craniofacial formation, it is postulated that there may be concomitant delayed skeletal development in association with missing teeth. However, growth is a process that shows wide individual variation and is difficult to predict. A number of methods have been used to assess growth including chronological age, dental developmental stage, peak height velocity, pubescent changes in the body and skeletal ossification events in the hand-wrist or cervical vertebrae.

The cervical vertebral maturation (CVM) index was developed using information from hand-wrist radiographs to estimate growth phases and develop standards for gender and age groups.[9] This index has also been used to investigate mandibular growth potential in the

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context of identifying pubertal growth spurts[10–14] and relating skeletal maturation to skeletal pattern.[15] The CVM index has yet to be used to investigate any possible link between skeletal maturation and tooth agenesis. This study examined differences in the cervical maturation stages between patients with tooth agenesis and controls to establish any differences in skeletal maturation and whether maturation varies with the severity of tooth agenesis. Any difference in skeletal development in patients with tooth agenesis could have implications with regard to the age these patients might receive dental implants. It would be necessary, however, to have further research using a range of measurement tools before any links between tooth agenesis and skeletal maturation could be made.

The null hypotheses were:

1. there is no difference in skeletal maturation in patients with and without tooth agenesis;
2. there is no difference in skeletal maturation between patients with mild, moderate or severe tooth agenesis.

A single-centre retrospective cross-sectional study of lateral cephalograms based in a teaching hospital was undertaken over a period of 20 months with patients recruited from a tooth agenesis patient database and orthodontic clinics.

The aims of this study were to investigate if there is a difference in skeletal maturation between tooth agenesis and control patients and whether skeletal maturation is affected by the severity of tooth agenesis.

Materials and methods

A total of 360 patients (164 males and 196 females) allocated to four subgroups (mild, moderate and severe tooth agenesis, and controls) were assessed retrospectively. The study was conducted using lateral cephalometric radiographs of patients who were either undergoing active orthodontic treatment or who had been discharged from the hospital. There were 90 patients in each group and all the cephalograms were taken as part of the patients' orthodontic records and were clinically justified. Ethical approval was granted for this study by University College London Hospitals Research and Ethics Committee (REC Reference Number: 09/H0715/83).

All patients were Caucasian and aged between 9 and 17 years at the time the lateral cephalometric radiograph was taken and all had a radiograph of good quality. The severity and distribution of tooth agenesis was confirmed from a dental panoramic tomograph present in the notes and by checking these findings with the clinical notes.

There were three groups to which patients were assigned on the basis of the number of teeth missing:[16–18]

- mild tooth agenesis (one to two teeth missing);
- moderate tooth agenesis (three to five teeth missing);
- severe tooth agenesis (six or more teeth missing).

By convention, third molars were excluded from the assessment.

Inclusion and exclusion criteria

- all patients were Caucasian and aged between 9 and 17 years of age at the time the lateral cephalogram was taken;
- all patients were either patients discharged from the hospital having completed treatment or active patients under treatment;
- all discharged patients had signed a consent form that gave their approval for the use of records for research, which was present within the notes. For active patients, a study consent form was signed for inclusion in the study;
- a lateral cephalogram and a dental panoramic tomograph of sufficient quality were present in the notes;
- those patients with a lateral cephalogram in their notes that had been taken at a different hospital were excluded due to uncertainty of the magnification of different cephalostats;
- those patients with radiographs that did not show a complete view of the three cervical vertebrae to be traced (C2 to C4) due to cone cutting were excluded;
- those patients with known ectodermal dysplasia or other syndromes were excluded.

The recruitment of patients for the study was initially from a departmental database. Additional patients were recruited from the orthodontic consultant clinic or the tooth agenesis clinic. The selected patients were provided with information about the study on an information sheet approved by the ethics committee. Informed consent was then gained and a consent form completed for each patient recruited. All unaffected control patients were recruited and consented on attendance to the orthodontic department.

The data were collected in two phases with phase one involving classifying the patient into the relevant subgroup (mild, moderate, severe tooth agenesis or control) followed by phase two where the cervical vertebrae were assessed. A single operator (CC) traced all radiographs in a darkened room, using the same light box throughout. The area surrounding the vertebrae on the radiograph was shielded with black card to exclude extraneous light and to obstruct the view of the

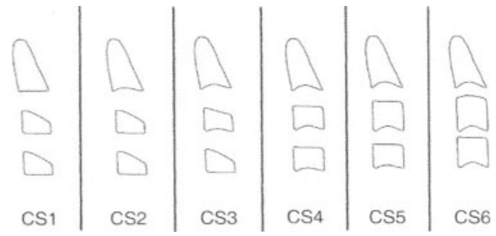

Figure 1 Schematic representation of the stages of cervical vertebral maturation 'Reprinted from The Cervical Vertebral Maturation (CVM) Method for the Assessment of Optimal Treatment Timing in Dentofacial Orthopedics, Vol. 11, Baccetti T, Franchi L and McNamara JA, Jr, 119–129 (2005), with permission from Elsevier'

dentition. Every patient was allocated a subject number so that the operator was blinded to the patient's subgroup to minimize bias. To avoid operator fatigue, no more than 10 radiographs were traced in any one session and a period of operator training commenced prior to the data collection.

The following qualitative and quantitative data were captured for each patient based on the CVM index previously described:[9]

Qualitative measurements (Figure 1):

- the shape of the vertebrae C3 and C4 (classified into one of four categories);
- a visual assessment of the shape of the C3 and C4 vertebrae involving inspecting the shape of the borders of the vertebrae (superior, inferior, medial and lateral borders) and classifying them into one of four categories (trapezoid, rectangular horizontal, square or rectangular vertical). The vertebrae are initially trapezoid and gradually progress to rectangular vertical as they grow with C3 generally maturing ahead of C4.
- the CVM stage achieved (classified into six cervical maturational stages from CS1 to CS6):

1. lower borders of all three vertebrae are flat and the bodies of C3 and C4 are trapezoid (CS1);
2. lower border of C2 has a concavity and the bodies of C3 and C4 are trapezoid (CS2);
3. concavities are seen at the lower border of C2 and C3 and the bodies of C3 and C4 are either trapezoid or rectangular horizontal in shape (CS3);
4. concavities are seen at the lower border of all three vertebrae and the bodies of C3 and C4 are rectangular horizontal (CS4);
5. concavities are seen at the lower border in all three vertebrae and at least one of the bodies of C3 or C4 are squared. If not a square shape the body of the other vertebra is rectangular horizontal (CS5);
6. concavities are seen at the lower border in all three vertebrae and at least one of C3 or C4 is rectangular vertical in shape. The other vertebra if not rectangular vertical is square in shape (CS6).

CS1 and CS2 make up the pre-peak stages while the peak in mandibular growth is thought to occur between CS3 and CS4. The final stage of CS6 occurs 2 years after the peak in growth has occurred.

Quantitative measurements (Figure 2):

- measurement of the concavity depth of C2, C3 and C4 (C2Conc, C3Conc and C4Conc);
- ratio of length of C3 base and anterior height (C3BAR);
- ratio of posterior and anterior height of C3 (C3PAR);
- ratio of length of C4 base and anterior height (C4BAR);
- ratio of posterior and anterior height of C4 (C4PAR).

There are 13 points in total that are plotted from the same lateral cephalogram from which the measurements are made. It is from these plotted points that three linear and four ratio measurements are made:

1. measurement of the concavity depth of C2 (C2Conc);
2. measurement of the concavity depth of C3 (C3Conc);
3. measurement of the concavity depth of C4 (C4Conc);
4. ratio of length of C3 base (C3lp–C3la) and anterior height (C3ua–C3la) (C3BAR);
5. ratio of posterior (C3up–C3lp) and anterior height of C3 (C3ua–C3la) (C3PAR);
6. ratio of length of C4 base (C4lp–C4la) and anterior height (C4ua–C4la) (C4BAR);
7. Ratio of posterior (C4up–C4lp) and anterior height of C4 (C4ua–C4la) (C4PAR).

All the linear measurements were made using the same ruler throughout and the units of all measurements made were in millimetres. The measurements could be made to the nearest half a millimetre using this measurement tool. The quantitative measurements were used to determine if there was a statistical difference in the dimensions of the vertebrae to indicate a difference in skeletal maturation. The qualitative data were used to determine the cervical maturation stage achieved. All linear measurements were corrected for magnification of the cephalograms and all measurements were carried out by one operator to minimize landmark identification error.[19]

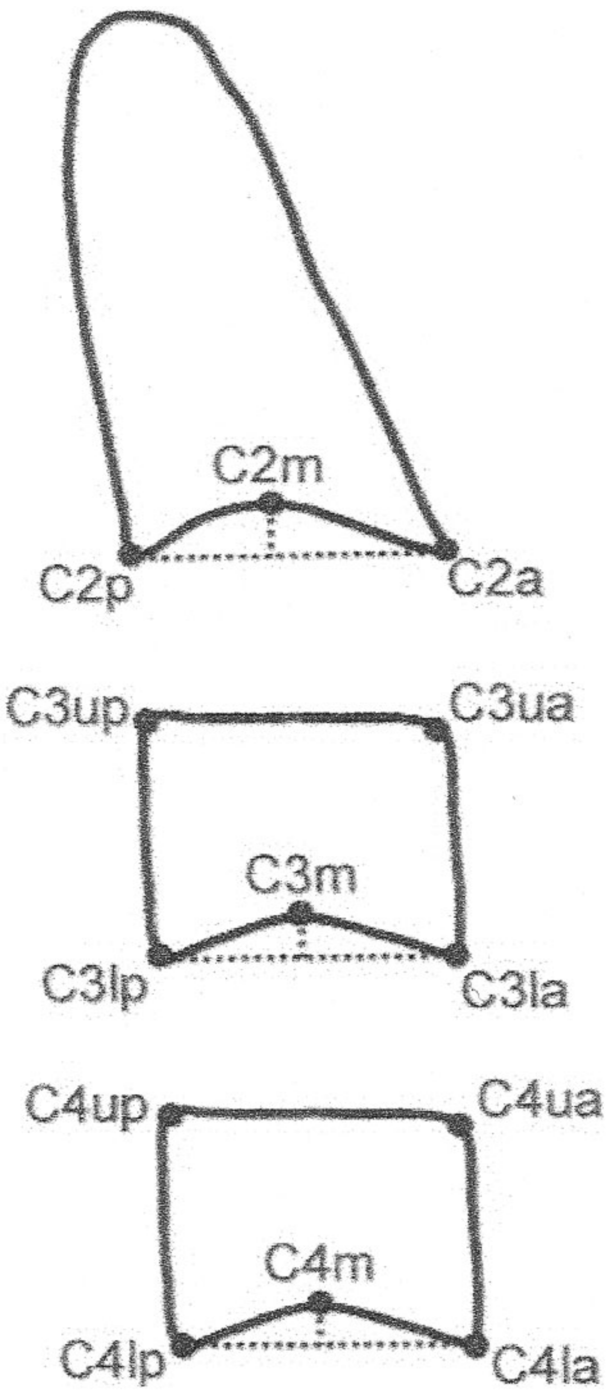

Figure 2 Cephalometric landmarks for the quantitative analysis of C2, C3 and C4 vertebrae. Reprinted from The Cervical Vertebral Maturation (CVM) Method for the Assessment of Optimal Treatment Timing in Dentofacial Orthopedics, Vol 11, Baccetti T, Franchi L and McNamara Jr JA, 119–129, (2005), with permission from Elsevier

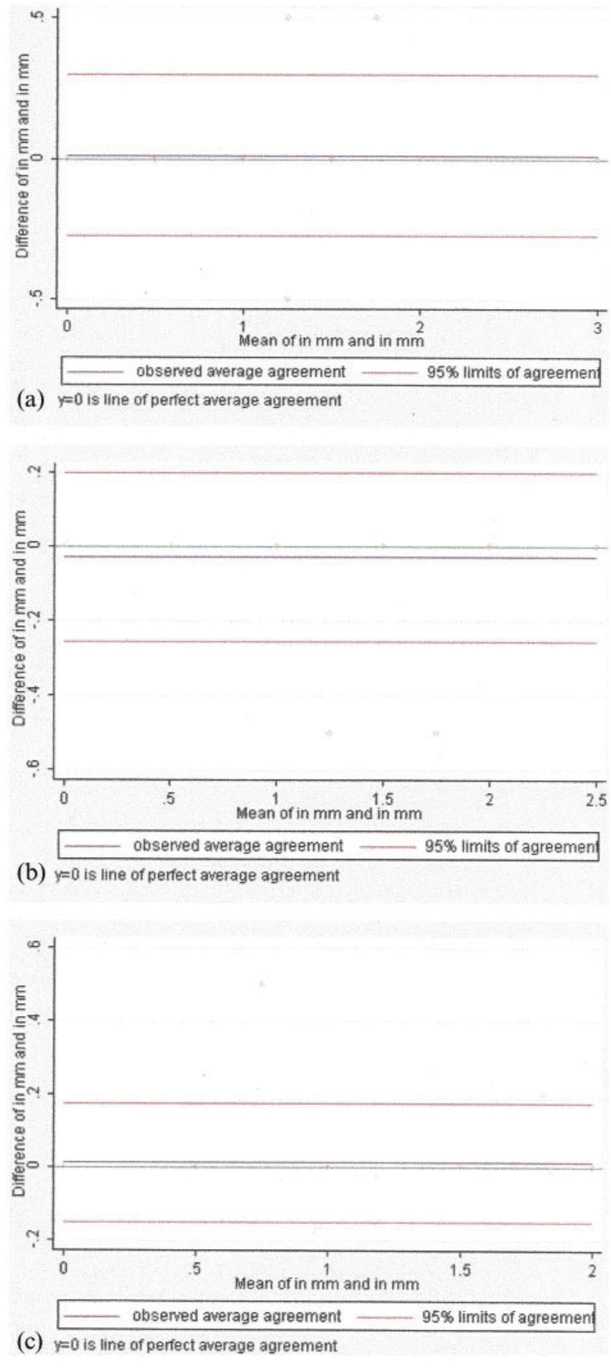

Figure 3 (a–c) Bland–Altman graphs for the quantitative linear measurements of C2Conc, C3Conc and C4Conc

A pilot study was carried out using 36 radiographs (10% of the total sample) with equal numbers of mild, moderate and severe tooth agenesis patients, and controls (nine patients in each group). The radiographs were traced and the data recorded before being retraced in a randomized order 2 weeks later to avoid landmark memorisation.[20] Following the second phase of the pilot study, statistical analysis of intra-observer error and repeatability were carried out.

A sample size calculation using nQuery advisor software™ (version 4.0 Statistical Solutions, Sangus, MA, USA) showed that a minimum sample size of 85 patients would be necessary within each group to detect a difference of 25 per cent in skeletal maturation between the mild tooth agenesis and the control groups at a power of 90% and significance level of 0.05. The sample sizes were rounded up to 90 within each subgroup to ensure that this power was achieved.

Repeatability (error) study

Intra-operator repeatability was assessed for the categorical data using Cohen's kappa and for the numerical data using the Bland–Altman method.[21]

The intra-operator repeatability was assessed using Cohen's kappa statistic and the values were as follows:

- shape of C3 (kappa value 0.89);
- shape of C4 (kappa value 1.00);
- CVM stage (kappa value 1.00).

A kappa score of 0.80 indicates good agreement between two sets of measurements while a score of 1.00 indicates perfect agreement. It can be seen from the results that good agreement was obtained for the C3 analysis and perfect agreement for the C4 analysis and the CVM stage. It can be concluded that for this study the repeatability was acceptable to a good or perfect level of agreement.

The Bland–Altman method allows for a visual analysis of the data via production of scatter grams. These are graphs of the mean of the paired readings (x-axis) plotted against the difference between the paired readings (y-axis). The method aims to show the true values and any measurement error within a 95% limit of agreement. Figures 3 A-C show the graphs for the quantitative linear measurements of the vertebrae for C2Conc, C3Conc and C4 Conc showing the differences between the two values obtained in the error study plotted against the mean values of the data. Figure 4 show the graphs for the quantitative ratio measurements for C3BAR, C3PAR, C4BAR and C4PAR. For the numerical data, there was an even fit of the points around the line of observed average agreement and an even scatter of the points was observed. There was no funnel effect seen (i.e. an even scatter of points) and the majority of the points fell within the 95% limits of agreement. This demonstrated acceptable repeatability.

Statistical analysis

All patients included in the pilot and main studies were anonymized using a numerical reference code when

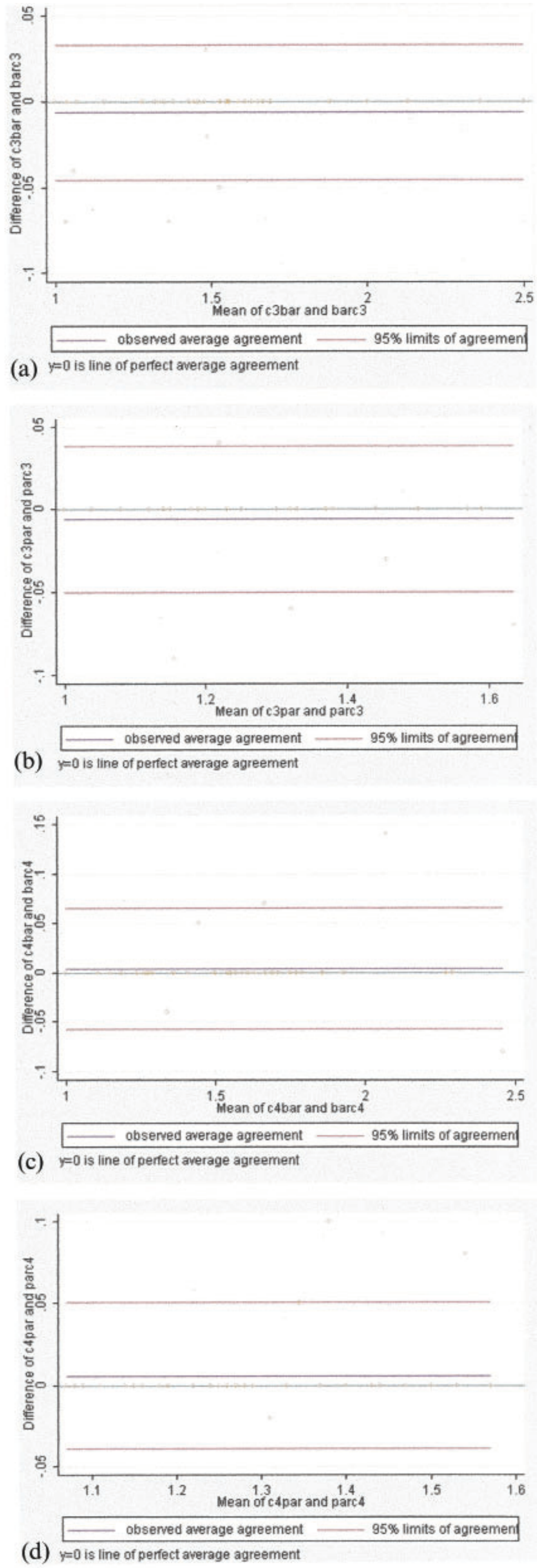

Figure 4 (a–d) Bland–Altman graphs for the quantitative ratio measurements of C3BAR, C3PAR, C4BAR and C4PAR

analysing and presenting the results. Intra-operator repeatability and data analysis were assessed using the statistical packages SPSS® software (Statistical Package for the Social Sciences, version 17.0) and Stata (Data Analysis and Statistical Software, version 10.0).

In order to assess the distribution of the data obtained in the study, one of the continuous variables was selected (C2Conc) and the values were plotted as a histogram. This variable was chosen as it was the largest of the three linear variables to be measured. The data was skewed to the left and was therefore not normally distributed. The median and the range were used to describe the data and non-parametric tests were used. The ages of the subjects and the linear depth of the vertebrae concavities were normally distributed. The mean and the standard deviation were used to describe the data and parametric tests were used. Statistical significance was inferred at $P<0.05$.

The ages of the subjects were compared with the study subgroups (mild/moderate/severe/control) using the *t*-test. Gender, study subgroups and CVM stages were analysed using the Chi-squared test.

The relationship between number of missing teeth and gender was investigated using the Mann–Whitney *U* test. All the quantitative ratio measurements of the vertebrae were analysed using the Kruskal–Wallis test as well as the subgroups, the number of missing teeth and CVM stages.

The Pearson correlation coefficient was used to compare age with the CVM stages and the linear measurements of vertebrae concavity with both the different subgroups and gender. The Spearman's rank correlation coefficient examined the study subgroups and CVM stages.

Results

All the patients undergoing treatment at the hospital who were recruited for the study agreed to participate and there were no withdrawals. There were a total of 270 tooth agenesis patients and 90 controls in the study.

Socio-demographic data: age and gender

Table 1 shows the age of the patients included in the study ranged from 9.08 to 16.92 years. This range was not statistically significant between the subgroups ($P=0.077$). The mean age range between the subgroups was 13.09–13.50 years and the age of the patients in the different study subgroups was normally distributed.

There was no statistically significant difference seen between the gender and the different subgroups ($P=0.463$). The male and female groups were comparable in terms of the number of missing teeth and this range of missing teeth was not statistically significant ($P=0.572$).

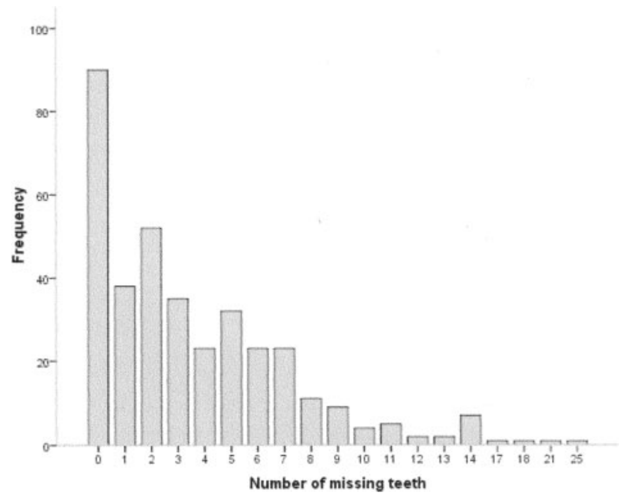

Figure 5 Distribution of developmentally missing teeth for all four subgroups within the study

Number of missing teeth

A histogram was constructed to illustrate the frequency of the number of missing teeth in the population studied (including the control patients) and is shown in Figure 5. The median number of missing teeth was three in the study group and the number of missing teeth ranged from 0 to 25. The median and range of missing teeth were very similar for the two genders showing that the genders were comparable. The relationship between gender and the number of missing teeth was not statistically significant ($P=0.572$).

CVM stages in the study population

Figure 6 illustrates the frequency of each maturation stage with separate columns for tooth agenesis and control patients in the study. The CS3 stage was the most frequently achieved stage with this stage marking the commencement of the pubertal growth spurt.

CVM stage compared with demographic data of the subjects

The data showed that as age increases the maturation stage increases, although there is natural variation in this process as illustrated in the range of ages seen from CS1 to CS6. The relationship between age and maturation stage is highly statistically significant ($P<0.001$). The box plot in Figure 7 illustrates the relationship between age and the different vertebral maturation stages.

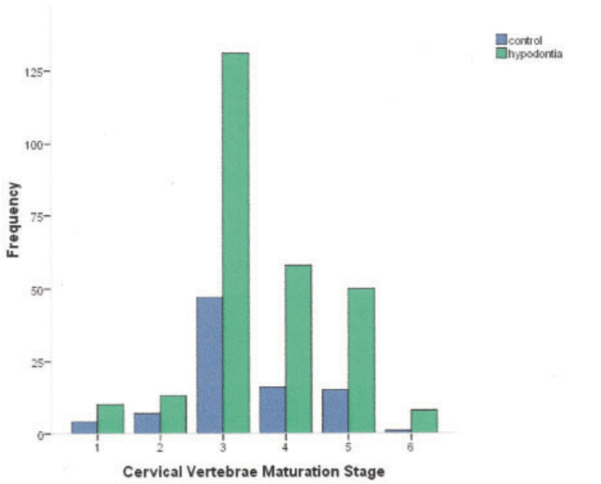

Figure 6 Frequency of each CVM stage for all four subgroups in the study

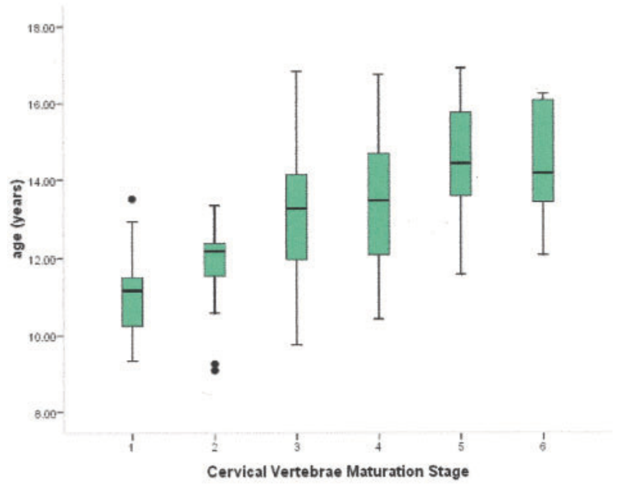

Figure 7 Box plot of age versus CVM stage for male and female patients

Table 2 shows the number of males and females within each of the CMV stages. Both genders achieved CS3 most frequently and therefore overall this was the most commonly achieved stage. The numbers of patients of each gender were approximately equal on stages CS3 and 4, whereas in CS1 and 2 there were more male patients and in CS5 and 6 more female patients. The female patients were reaching the CVM stages earlier than the male patients. The relationship between gender and CVM stage was highly statistically significant ($P<0.001$).

CVM stage and the distribution of tooth agenesis patients and controls

Direct comparison between the control and tooth agenesis patients is possible through the use of the percentage of the total group achieving each maturational stage. In each of the CVM stages, the percentage of tooth agenesis and control patients were similar (e.g. stage CS3 was achieved by 48.5% tooth agenesis patients and 53.3% of controls). In both the control and tooth agenesis subgroups, the most commonly achieved maturation stage was CS3. There was no significant difference in CVM stage between the control and tooth agenesis groups ($P=0.193$). Table 3 summarizes the numbers of patients in the tooth agenesis and control groups within each maturation stage.

It is evident when looking at the most commonly achieved maturation stage (CS3) that just as many patients affected by different severities of tooth agenesis reached this stage as did the control patients not affected by tooth agenesis. There were higher numbers of patients reaching CS4 who had severe tooth agenesis than were part of the control group. There was no statistical difference between the subgroups (tooth agenesis and controls) and the CVM stage ($P=0.055$). Table 4 summarizes the numbers of mild, moderate and severe tooth agenesis patients that were found in each maturation stage.

CVM stage and number of missing teeth

The median numbers of missing teeth in each group were comparable between the groups and there was no

Table 1 The age distribution within the study group.

Age (years)		Severity of tooth agenesis		
	Control	Mild	Moderate	Severe
Mean	13.09	13.43	13.50	13.39
Standard deviation	1.63	1.40	1.76	1.82
Minimum	9.92	9.83	9.08	9.25
Maximum	16.75	16.58	16.83	16.92

$P=0.077$, *t*-test.

Table 2 The gender distribution within the different CVM stages (CS1–CS6).

	CS1	CS2	CS3	CS4	CS5	CS6	Total
Male	12	13	87	36	15	1	164
Female	2	6	92	38	50	8	196
Total	14	19	179	74	65	9	360

$P<0.001$, Chi-squared test).

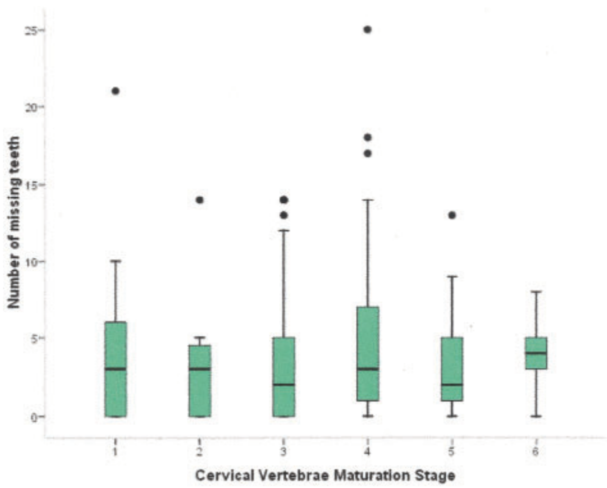

Figure 8 Box plot of the number of missing teeth versus the CVM stage

pattern seen with the increase in maturation of the vertebrae. The range of missing teeth showed no pattern with maturation stage. This data are represented graphically in Figure 8. There was no statistically significant difference seen in CVM stages between the tooth agenesis severity subgroups ($P=0.487$).

Quantitative ratio measurements of the vertebrae

C3BAR (C4BAR) is the ratio of the base of C3 (C4) and the anterior height of the vertebrae while C3PAR (C4PAR) is the ratio of posterior to anterior height of C3 (C4) (Figure 2). C3BAR, C3PAR, C4BAR and C4PAR both reflect the dimensions of the vertebrae and permit quantitative assessment of the different sizes of the vertebrae within the groups. This quantitative measurement is independent of the CVM index and is not used in staging the vertebrae.

For both C3BAR and C3PAR, there was no obvious pattern seen in the size of C3 with different severities of tooth agenesis and in the absence of tooth agenesis. There was no statistically significant difference seen ($P=0.094$ for C3BAR and $P=0.225$ for C3PAR). For both C4BAR and C4PAR there was no obvious pattern seen in the size of C4 with different severities of tooth agenesis and in the absence of tooth agenesis. There was also no statistically significant difference seen ($P=0.210$ for C4BAR and $P=0.349$ for C4PAR) (Figure 9).

Quantitative linear measurements of the vertebrae

There were three linear measurements made of the concavities of C2, C3 and C4 (C2Conc, C3Conc and C4Conc) in the study to allow for additional quantitative analysis. All linear measurements were corrected for radiographic magnification. The qualitative aspect of this feature (i.e. the presence or absence of a concavity) is used in the CVM index staging process.

C2Conc and C3Conc had identical medians (0.93 mm) and ranges of concavity (0.00–2.79 mm), which meant that the data generated for these two variables were comparable. The data for C4Conc had a marginally smaller median (0.91 mm) and range of concavity (0.00–2.33 mm). Both C2 and C3 have concavities formed at the base of their vertebrae when C4 begins to form and this is the basis of the vertebral development and the CVM index.

The results for C2 and C3 both showed that females were slightly more advanced in their development compared to males. For C4, the females were advanced to a greater degree in their development (Figure 10). The relationship between the concavity measured for the three vertebrae and gender was statistically significant ($P<0.001$).

C2Conc showed a congruous range in the size of the concavity of the vertebrae in the three tooth agenesis subgroups. The control group showed less variation in size, but had more outliers that fell above or below the general range of results. C3Conc seemed to be of similar

Table 4 Distribution of the CVM index within the study subgroups.

Subgroup	CS1	CS2	CS3	CS4	CS5	CS6	Total
Control	4	6	48	16	15	1	90
Mild	1	2	49	19	18	1	90
Moderate	5	10	41	13	16	5	90
Severe	4	1	41	26	16	2	90
Total	14	19	179	74	65	9	360

$P=0.055$, Chi-squared test).

Table 3 Distribution of the CVM stages within the control and tooth agenesis groups.

Subgroup	CS1	CS2	CS3	CS4	CS5	CS6
Control, % (*n*)	4.44% (4)	6.67% (6)	53.3% (48)	17.8% (16)	16.7% (15)	1.11% (1)
Tooth agenesis, % (*n*)	3.70% (10)	4.81% (13)	48.5% (131)	21.5% (58)	18.5% (50)	2.96% (8)

$P=0.193$, Chi-squared test.

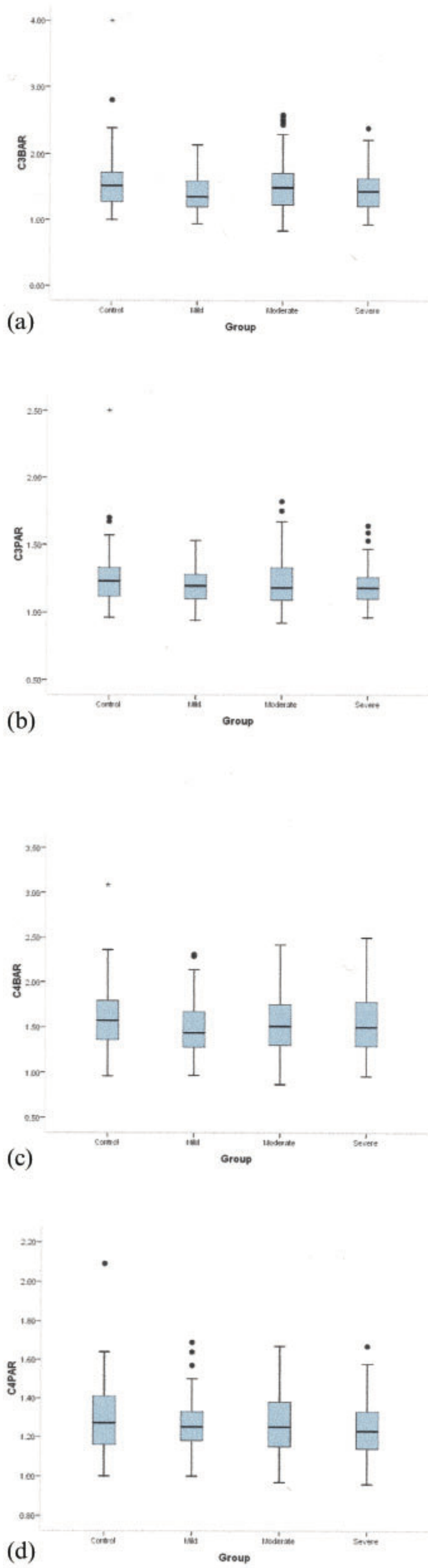

Figure 9 (a–d) Box plots of ratios of C3BAR, C3PAR, C4BAR and C4PAR versus the type of tooth agenesis

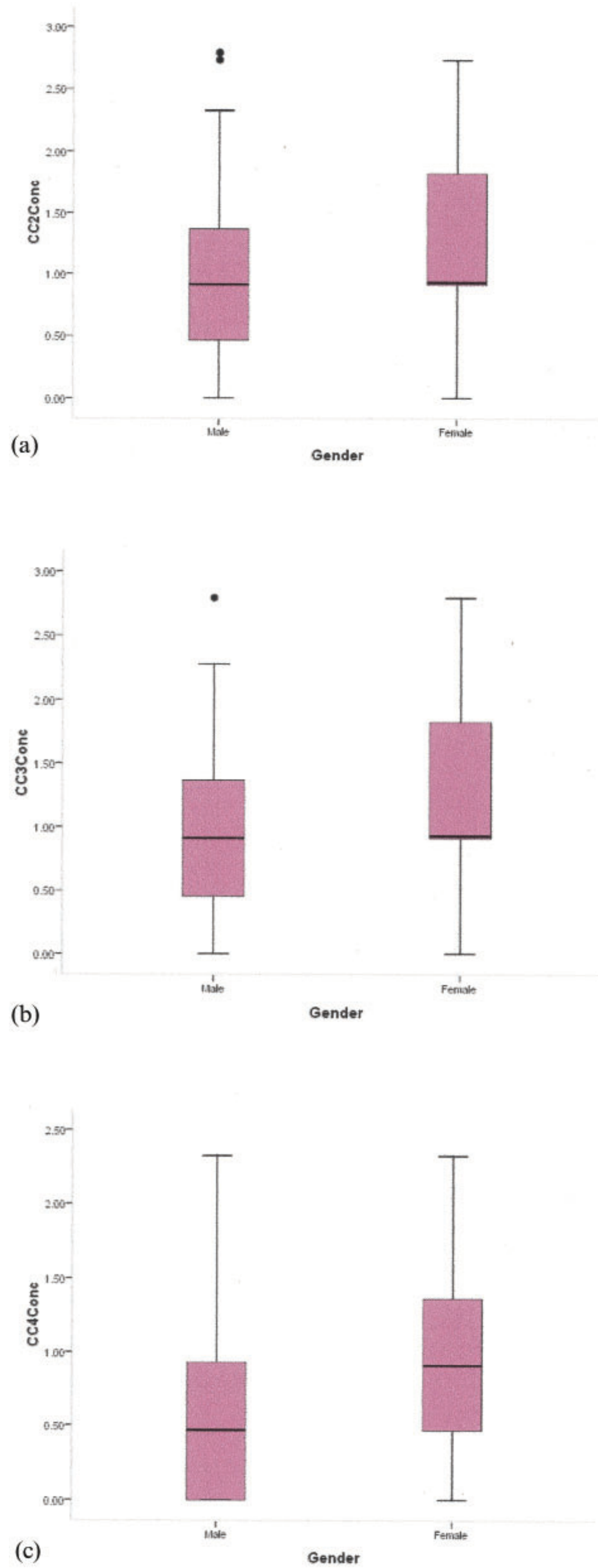

Figure 10 (a–c) Box plots of CC2Conc, CC3Conc and CC4Conc versus gender

size in all four subgroups with the control groups having a slightly smaller range of values. C4Conc showed the most variation both in size of the concavity of C4 but also between the groups (Figure 11). None of the linear measurements showed a statistically significant relationship with the different subgroups ($P=0.238$ for C2Conc, $P=0.913$ for C3Conc and $P=0.968$ for C4Conc).

Linear measurements were compared with different CVM stages (Figure 12) showed that:

- in CS1, the vertebrae of C2 to C4 are flat and therefore there are no measurements on the graph;
- in CS2, the vertebrae of C3 and C4 are flat and only C2 has a concavity present;
- in CS3, there are concavities present in the lower border of C2 and C3;
- CS4, CS5 and CS6 have concavities present at the base of all three vertebrae.

As the CVM stage increases, the length of the concavity at the base of the vertebrae (see dotted lines to indicate a linear measurement on Figure 2) increases and there is a maximum in the length achieved once the vertebrae achieve the post pubertal stages of CS5 and CS6. There was a statistically significant relationship between the CVM stage and the linear measurements for all three vertebrae ($P<0.001$).

Discussion

This age range of patients was chosen based upon a previous study using the CVM method to investigate longitudinal growth changes in class II subjects.[22] In this study, the patients achieving CS1 had the mean age of ten years (SD: 1.5 years) and for CS6, they had the mean age of fifteen and a half years (SD: 1.5 years). This meant that the maximum mean age range for which it was possible to measure CS1 to CS6 ranged from eight and a half years to 17 years. There was a 1 : 1 gender ratio seen in all subgroups with the exception of the mild tooth agenesis subgroup where a 3 : 2 ratio of females to males. As there was no statistically significant difference seen between the genders and the different subgroups ($P=0.463$) and between the genders and the numbers of missing teeth ($P=0.572$), the genders were combined in the subsequent statistical analysis.

CS3 was the most frequently seen maturation stage in the study population (49.7%) and is the stage that marks the commencement of the pubertal growth spurt.[9] If the stages are looked at in terms of pre-pubertal, pubertal and post-pubertal phases then the most common stage is the pubertal phase (CVM stages CS3 and CS4) with

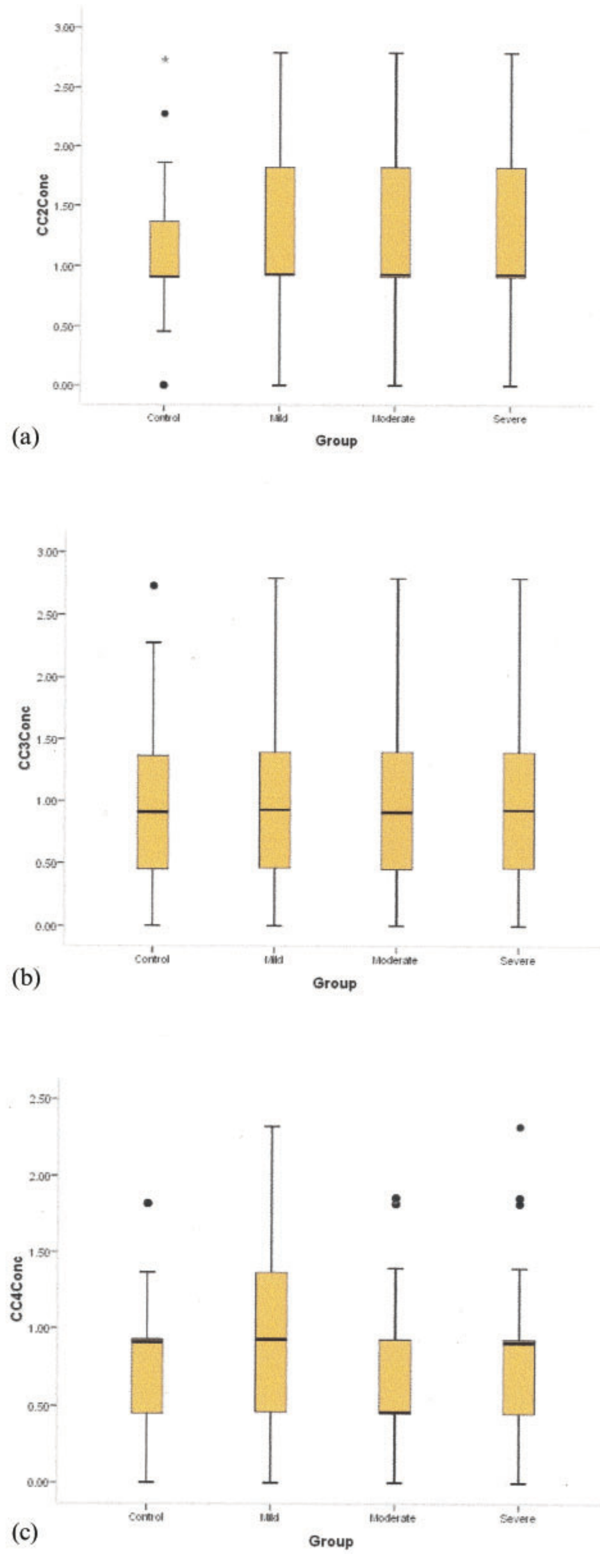

Figure 11 (a–c) Box plots of CC2Conc, CC3Conc and CC4Conc versus severity of tooth agenesis

70.3% of the sample. This finding was not unexpected, as the majority of patients commencing orthodontic treatment, which is when the lateral cephalograms were taken, would be expected to be in the pubertal phase.

The relationship between age and CVM stage proved to be statistically significant and it was observed that with increase in age, the CVM stage increased ($P<0.001$). The maturation stages represent stages of the growth of the individual and it is expected that as the individual gets older, the stage will increase. It has been concluded in many studies that CVM correlates well with age and pubertal growth spurt.[9–11,13,14]

Female patients achieved each CVM stage slightly earlier than males. The ratio of male and female patients between the CVM groups was approximately 1 : 1 for the CS3 and CS4 stages (the most commonly achieved stages). There were more males in CS1 and 2 and more females in CS5 and 6. This can be explained by the fact that females reach their growth spurt earlier than males[23] and thus, the post-pubertal maturation stages of CS5 and CS6 are most likely to be heavily female populated.[11,13] The relationship between CVM stage and gender was statistically significant ($P<0.001$). The results suggest that females were more advanced in their development and this explains why gender standards were developed for the CVM index. A previous study comparing cervical maturation stages and standing height showed that girls matured earlier than boys and the female group had reached adult levels of maturity by 15 years.[11]

When compared to controls, patients with tooth agenesis did not have a statistically significant difference in their vertebral development ($P=0.193$). The numbers of patients observed at each CVM stage in the tooth agenesis and control groups were comparable. There was no statistically significant difference associated with the severity of tooth agenesis ($P=0.055$). The mean ages of the patients in the different subgroups were congruous, and hence, age is unlikely to influence the CVM staging within each group and subgroup.

The median number of missing teeth seen in each CVM stage ranged from two to four teeth. The box plot in Figure 8 showed that there was no direct relationship between the CVM stage of the subject and the number of missing teeth, and that there was no statistical difference between the groups ($P=0.487$).

The CVM index has been used in previous studies to look at patients undergoing growth dependent treatments with as functional appliances but it has not been used to date to look at tooth agenesis. The CVM index has been used to investigate mandibular growth potential in the context of identifying pubertal growth spurts[10–14] and relating skeletal maturation to skeletal pattern.[15]

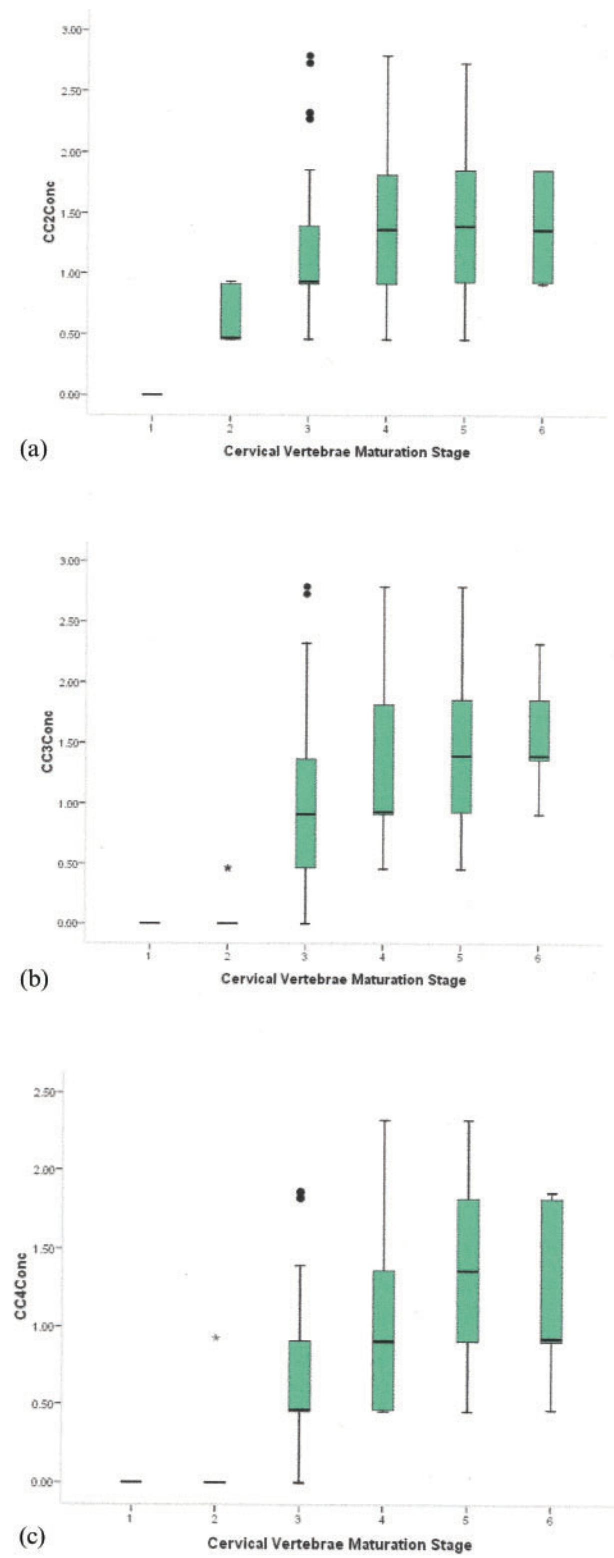

Figure 12 (a–c) Box plots of CC2Conc, CC3Conc and CC4Conc versus CVM stage

The strength of this study included the large sample size and the inclusion of equal numbers of the different severities of tooth agenesis, despite there being significantly different levels of prevalence of mild, moderate and severe tooth agenesis in the population. Hence, the study design was effective in minimising any prevalence bias that might have otherwise existed.

The CVM method has received recent criticism in a study that claimed the method had poor reproducibility and needed to be used in conjunction with other indicators for guidance with the timing of orthodontic treatment.[24] In contrast, the current study concluded that the CVM method had good reproducibility, although the statistics used for the quantitative data were different to those used in previous study so comparison between the two is difficult. It must be accepted that this is one method of assessing skeletal maturation and it was not the aim of this study to compare various methods.

The limitations of the study are as follows:

- the genders were combined in the statistical analysis because there were no statistical significant differences seen between gender and the study subgroups ($P=0.463$) or between gender and the numbers of missing teeth ($P=0.572$). However, as there was a statistically significant seen between gender and CVM stages ($P<0.001$). This was to be expected as CVM stage is a measure of skeletal development and it is known that the females reach maturity at a faster rate than males. There is, however, a risk of false positive results the greater the number of statistical comparisons made;
- linear measurements: although it is possible that any differences in the linear measurements could be masked by the degree of error in measurement, this would not affect the maturation index interpretation and staging of the CVM index;
- vertebrae imaging: slight tipping of the vertebrae when the radiograph was taken could change the degree of convexity. Again this will not affect the CVM index interpretation, but means that the linear measurements should be interpreted with caution.

Operator error was kept to a minimum by:

- errors in landmark identification: these were minimized by operator calibration prior to commencement of data collection. The measurements were carried out by one investigator to minimize errors;
- measurement errors: these were assessed by the repeatability (error) study that was conducted before data collection;
- projection errors (magnification factors) affecting linear measurements which were corrected for prior to statistical analysis.

Clinical significance

The results of the study showed that there was no cephalometrically measurable difference using this measurement tool and study population in skeletal development between the tooth agenesis patients and controls. If the study population is representative of the wider population, then it is possible that tooth agenesis patients may not have a delay in skeletal development. This can only be stated as a possibility as a direct extrapolation is not possible without further research.

Studies have made a link between the MSX family of genes and their roles in both tooth and craniofacial formation.[4–7] It is possible that there may not be a direct link between the two and that further research to aid our understanding of the genetics is necessary.

It is important to state that there are many ways of assessing growth and that this study used one specific method to assess skeletal maturation to test the null hypothesis. It is not possible to offer definitive conclusion that no difference exists either between patients with tooth agenesis and controls or between the different severities of tooth agenesis only a suggestion that it is possible that a difference may not exist.

Conclusions

Both age and gender were found to have a statistically significant relationship with the CVM stages with increasing age correlating with increasing maturation stages and females maturing faster than males. The vertebrae also showed more advanced development in females compared with males.

The CVM stages did not have a statistically significant relationship with tooth agenesis or control patients nor was there any relationship with the different severities of tooth agenesis. There was no statistically significant relationship with either increasing age or gender and the severity of tooth agenesis. In addition to this, there was no statistically significant difference and the development or size of the vertebrae.

The following conclusions can be drawn from the subjects studied and the measurement tool used:

- there was no detected difference in the skeletal maturation between patients with and without tooth agenesis;

- there was no detected difference between the skeletal maturity of those patients with different severities of tooth agenesis.
- the data obtained from using this method therefore do not supply sufficient reason to reject the null hypothesis; however, it suggests that it is possible that no difference exists between the groups.

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